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MATHEMATICAL MODELS OF CHEMOTHERAPY

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1. Introduction

Suppose one injects a drug into an animal. What is the time course of the drug concentration in the blood and in the various organs of the body? Although preliminary attempts to set up mathematical models of this problem were made by Teorell [1], [2] and models of certain special cases have been considered by von Schrotter [3], Smith and Morales [4], and Morales and Smith [5], [6], it continues to challenge the biologist and mathematician. Much of the recent theoretical work in this area has been concerned with the analysis of radioactive tracer experiments on compartmentalized systems assumed to be in a steady state [7], [8]. This leads to the usual sets of simultaneous linear differential equations. We wish to consider the more complex kinetic problem. In particular, we wish to consider the kinetics of distribution of an injected compound assuming that it exchanges between capillary plasma and extracellular space by diffusion, enters the intracellular space by diffusion and perhaps by some active transport process and can react with some constituent (say an enzyme) of the intracellular space. Although the motivation for studying this problem was the desire to obtain a theoretical framework for the analysis of results with various agents used in cancer chemotherapy, the problem is of more general importance for physiology and pharmacology.

2. Anatomical and physiological considerations

Any mathematical model of such a complex process must be firmly imbedded in the known anatomical and physiological background if it is to approach

reality. Let us therefore review briefly the basic anatomy and physiology of the capillary circulation.

A tissue or region of an organ which we will be concerned with consists of many living cells. Most of the cells of any particular tissue have roughly similar shapes and sizes. Between the cells is a watery fluid, the extracellular fluid. Each cell is bounded by a cell membrane which is lipoprotein in nature. The lipid layer of the cell membrane acts as a barrier to the diffusion of polar molecules into the cell: so much so that, for polar molecules, diffusion across the cell membrane is orders of magnitudes slower than diffusion across an aqueous layer of comparable thickness. The blood supply to such a region enters via arteries which branch and eventually give rise to the precapillary arterioles. The arterioles give rise to many small tubules whose walls consist of a single thin layer of flat cells. These are the capillaries which pass through the extracellular space and finally join to form venules which combine to form the veins which carry the blood away from the region. According to Zweifach [9], [10], there are preferred channels, A-V bridges, connecting arterioles and venules and many of the capillaries arise from these A-V bridges. These A-V bridges have muscle cells at various points of their walls which presumably function in the regulation of the capillary circulation. With low blood flows to a region, the main flow is through the A-V bridge. As the flow increases, more and more of the flow passes through the capillaries arising from the A-V bridge. Thus increased blood flow is to a great extent accommodated by an opening of more channels and not simply by an increased flow rate in a fixed number of channels. It follows that as total flow through a capillary bed increases, the surface area and volume of the capillary bed increase. The capillaries in any region are fairly uniformly distributed with their flows in many directions, although some orientation may be imposed by the shape of the cells of a region, as in skeletal muscle where most of the capillaries run parallel to the large striated muscle cells. The number of capillaries through which blood is flowing may vary considerably, depending on the state of the tissue. Capillary flow in many regions is intermittent so that there is a rotation of function among the various capillaries of the region. Furthermore, there are many interconnections between capillaries so that one cannot think in terms of many single channels but must think in terms of a meshwork arising from a precapillary arteriole and A-V bridge and eventually draining into a venule. This meshwork is further interconnected with the meshworks arising from other precapillary arterioles. In many tissues one also finds arteriovenous shunts which bypass the capillary beds.

Although there is some variation in capillary dimensions, the average dimensions commonly quoted in the literature are a radius of .0004 cm. and a length of .04 cm. The blood flowing through the capillaries consists of a suspension of cells in a fluid, the plasma. The exchanges we will be concerned with will be primarily between the plasma and extracellular space, so we will speak in terms of the plasma flow to a region.

To complicate our problem further, we must consider the effects of recircula-

tion and of mixing in the heart and vessels. Normally, blood flow in most vessels involves an almost uniform velocity flow of a central core containing the suspended cells. The major part of the shear occurs in a peripheral zone of suspending medium, the plasma. This is much like a volume displacement flow. We shall therefore assume a volume displacement flow with complete mixing in a direction perpendicular to the flow through a vessel. Further mixing will also occur in the heart. This allows us to concentrate on the effects introduced by the time lags inherent in the recirculation.

3. A mathematical model: general considerations

In view of these considerations, what sort of models of the processes occurring in the capillary bed might we consider?

Right at the outset we can discard the possibility of setting up the complete deterministic equations for a region. This would require complete knowledge of the geometrical relationships between all cells, extracellular fluid and all capillaries in the region. Even were this available for one particular area of one particular animal it would hardly lead to tractable equations. One might consider using average values for cell size, intercellular distance, capillary dimensions, and intercapillary distance, but this would not make the problem any easier. Another possibility, which has been suggested, is to treat a region as consisting of a group of domains, each domain consisting of a cylindrical region surrounding a capillary. Aside from the problem of choosing appropriate boundary conditions and solving the complex partial differential equations involved, there is the basic objection that this may be an inappropriate model. As was pointed out in the previous section, the capillary bed must be viewed as a meshwork of interconnecting capillaries and not a series of single channels connecting arterioles and venules. Since point by point measurements of the concentration of a compound in extracellular space and plasma are unavailable, all of these formulations seem needlessly complex. A macroscopic viewpoint may be more useful. For polar molecules we assume a uniform concentration in the extracellular space and in the intracellular space. These assumptions are justified by the following considerations: at least from a macroscopic viewpoint the fairly uniform distribution of capillaries and capillary flows and the intermittency of capillary action tends to smooth out diffusion gradients in the extracellular space. Furthermore, the diffusion of polar molecules across cell membranes into the intracellular space is much slower than diffusion across the capillary membrane into the extracellular space, and the latter is much slower than diffusion within the extracellular space [11], [12], [13]. In essence then, we use a spatial average for the extracellular concentration and the above considerations at least give us some assurance that the deviations from this mean value will not oscillate violently as one moves from point to point in the extracellular space.

It remains then to discuss how one can treat the capillary bed in view of the above assumptions. If the flow rate and cross sectional area for the various capil-

laries of the mesh have narrow distributions, we can lump the capillaries of a mesh into one capillary with the total surface area and plasma volume of the mesh and a length determined by the mean transit time for the mesh.

Thus our model of a capillary bed consists of a number of fairly simple functional units, each unit being the capillary mesh arising from a precapillary arteriole. These units are connected to the circulation in a parallel arrangement. Having obtained the solution to the equations for one unit, we then need only sum over all the units in the region under consideration in order to find the amount of drug in intercellular space, extracellular space and the amount of drug entering and leaving the region via the circulation. For the time being, however, we defer consideration of this last statistical aspect of the problem, since it will needlessly complicate matters in this stage of the investigation. For the time being we commit ourselves to the use of a mean value model.

4. Notation

To reduce some of the foregoing ideas to mathematical form, let us introduce the following definitions:

$u(x, t)$ = concentration of drug in moles per unit volume at x in the capillary at time t.

$v(t)$ = mean concentration of drug at time t in extracellular space.

$w(t)$ = concentration of free drug in intracellular space.

$z(t)$ = concentration of drug-enzyme complex ED resulting from reaction $E + D \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ED$ in intracellular space.

E_0 = total concentration of enzyme in intracellular space.

k_1, k_2 = rate constants for reaction of drug with E.

k_e = permeability constant for capillary walls.

k_i = permeability constant for cell membrane.

K = transport constant. Net active transport into the intracellular space is assumed to be given by KA_iv. This is only an approximation for most active transport systems.

c = volume flow rate of plasma in capillary bed.

l = mean capillary length.

R_p = plasma volume of capillary bed.

R_e = volume of extracellular space.

R_i = volume of intracellular space.

5. A model of a capillary bed

Following the remarks of section 3, we may diagram our model of the capillary bed as shown in figure 1.
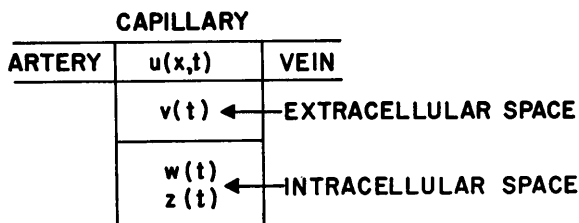
CAPILLARY

ARTERY	u(x,t)	VEIN

v(t) ◄──EXTRACELLULAR SPACE

w(t)
z (t) ◄──INTRACELLULAR SPACE

FIGURE 1

Model of capillary bed.

$u(x, t)$ = concentration of drug in moles per unit volume at x in the capillary at time t,

$v(t)$ = mean concentration of drug at time t in extracellular space,

$w(t)$ = concentration of free drug in intracellular space,

$z(t)$ = concentration of drug-enzyme complex ED resulting from reaction $E + D \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ED$ in intracellular space.

By standard arguments we obtain the set of equations

(1)
$$\frac{R_{pj}}{l} \frac{\partial u_j}{\partial t} = -c_j \frac{\partial u_j}{\partial x} - \frac{k_e A_{ej}}{l} (u_j - v_j),$$

(2)
$$R_{ej} \frac{dv_j}{dt} = \frac{k_e A_{ej}}{l} \int_0^l u_j(x, t)\, dx - k_e A_{ej} v_j - k_i A_{ij}(v_j - w_j) - K_j A_{ij} v_j,$$

(3)
$$R_{ij} \frac{dw_j}{dt} = K_j A_{ij} v_j + k_i A_{ij}(v_j - w_j) - k_1 R_{ij} w_j(E_{0j} - z_j) + R_{ij} k_2 z_j,$$

(4)
$$\frac{dz_j}{dt} = k_1 w_j(E_{0j} - z_j) - k_2 z_j.$$

The subscript j is present since we wish to speak of more than one capillary bed.

This is a particularly interesting set of equations, consisting of a partial differential equation, an integrodifferential equation, and two nonlinear, first-order, ordinary differential equations. We should point out that from the viewpoint of the experimenter, we do not need $u(x, t)$ but only the values of $u(0, t)$ and $u(l, t)$. These are the quantities which are measurable in practice. It should further be added that these equations are incomplete as they stand; we must still add equations which describe the effects of the circulation and the time course of drug administration. The former will link the output and input concentrations to the capillary bed via the time lags involved in recirculation and the mixing in the circulation.

6. A model of a two-organ being

As an introduction, let us consider a simplified organism (figure 2) which consists of two organs connected in parallel to the circulation, which is maintained by a simplified heart. Each of the boxes in figure 2 represents an organ. The

processes occurring in each organ are governed by equations (1) through (4), with j taking on the values 1 and 2 respectively. To these we must add the equations of the circulation and of drug injection. Let us assume that the drug is given intravenously. For simplicity we will treat the injection as though it were
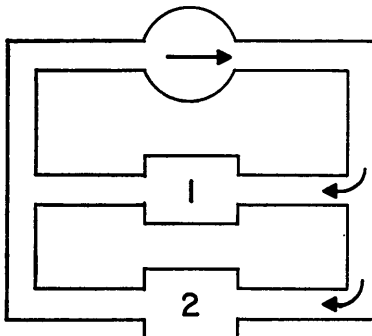

FIGURE 2

Diagram of a simplified organism with its two organs
connected in parallel to its circulation.

given directly at the entrance to the heart, then the concentration entering the heart will be

$$(5) \qquad u_R(t) = \begin{cases} 0, & t < 0, \\ u_I(t), & 0 \leqq t < \tau, \\ u_I(t) + \dfrac{c_1 u_1(l, t - \tau) + c_2 u_2(l, t - \tau)}{c}, & t \geqq \tau, \end{cases}$$

where τ is the circulation time lag from the exit of the capillary beds to the entrance to the heart, $u_I(t)$ describes the concentration of drug due to the injection, and the final term is the drug concentration resulting from recirculation. We are assuming that τ is the same for both organs.

The heart is treated as a mixing chamber of volume

$$(6) \qquad V^* = \frac{V_E}{[\log (1 + V_R/V_E)]},$$

where V_E is the ejection volume and V_R the residual volume of the heart [14], then the concentration of drug u_L in the plasma leaving the heart is given by

$$(7) \qquad u_L(t) = \begin{cases} 0, & t < 0, \\ \dfrac{c}{V^*} e^{-ct/V^*} \displaystyle\int_0^t u_R(y) e^{cy/V^*} \, dy, & t > 0. \end{cases}$$

Finally, the concentration of drug entering the capillary beds will be

$$(8) \qquad u_j(0, t) = \begin{cases} 0, & 0 \leqq t < \tau, \\ u_L(t - \tau), & t \geqq \tau. \end{cases}$$

It is apparent now that these conditions make our set of differential equations a set of differential difference equations.

7. Computations

The equations obtained so far present enormous analytical difficulties. Although the steady state may be obtained on physical grounds it is the time course during the early phases of the process which we will need if we wish to examine such problems as the relative value of direct intra-arteriol injection of a chemotherapeutic agent.

We can circumvent some of these difficulties if we can simplify the x-dependence in equation (1). A simple approximation to make is to assume that the concentration along the capillary will be linear in x. With this assumption equations (1) and (2) reduce to equations (9) and (10).

$$(9) \qquad \frac{R_{pj}}{2}\left(\frac{du_{j0}}{dt} + \frac{du_{jl}}{dt}\right) = c_j(u_{j0} - u_{jl}) - k_e A_{ej}\left(\frac{u_{j0} + u_{jl}}{2} - v_j\right)$$

$$(10) \qquad R_{ej}\frac{dv_j}{dt} = k_e A_{ej}\left(\frac{u_{j0} + u_{jl}}{2} - v_j\right) - k_i A_{ij}(v_j - w_j) - K_j A_{ij}v_j.$$

In these equations u_{j0} and u_{jl} represent the concentrations in the plasma entering and leaving capillary bed j.

This approximation will obviously be poor for processes of duration less than the capillary mesh mean transit time; this is particularly true for those periods when a concentration wave is entering or leaving the capillary bed. If we consider the start of the process when a concentration wave is entering the capillary bed, we have

$$(11) \qquad\qquad u_{jl}(0) = v_j(0) = 0, \qquad\qquad t = 0,$$

and equation (8) reduces to equation (11),

$$(12) \qquad \frac{du_{jl}(0)}{dt} = \frac{2}{R_{pj}}\left[c_j - \frac{k_e A_{ej}}{2}\right]u_{j0}(0) - \frac{du_{j0}(0)}{dt}.$$

Thus if $du_{j0}(0)/dt = 0$ then $du_{jl}(0)/dt < 0$ if $k_e A_{ej} > 2c_j$, giving negative values for $u_{jl}(t)$ for some short interval at the start of the process. On the other hand, if $du_{j0}(0)/dt > 0$ then $du_{jl}(0)/dt$ can still be negative for some values of $k_e A_{ej} < 2c_j$. This model has been programmed for the IBM 704 [15] and, as expected, has given negative concentration waves in the plasma which were propagated for some time because of the recirculation. Except for plasma concentration waves which change very slowly and for the condition $k_e A_{ej} < 2c_j$, this is a poor approximation.

To avoid the difficulties introduced by the above approximation, the capillary bed can be replaced by n mixing chambers in series, each of volume R_{pj}/n as shown in figure 3. This leads to the set of equations (13) and equation (14) in place of equations (1) and (2) respectively.

$$(13) \qquad \frac{du_{jm}}{dt} = \frac{nc_j}{R_{pj}} (u_{j,m-1} - u_{jm}) - \frac{k_e A_{ej}}{R_{pj}} (u_{jm} - v_j), \qquad m = 1, 2, \cdots, n,$$

$$(14) \qquad R_{ej} \frac{dv_j}{dt} = \frac{k_e A_{ej}}{n} \sum_{m=1}^{n} (u_{jm} - v_j) - k_i A_{ij}(v_j - w_j) - K_j A_{ij} v_j.$$

This approximating model has the advantage that negative solutions cannot be obtained and that equations (13) and (14) converge on (1) and (2) respectively as n increases. Furthermore, we expect on physical grounds that we need only make n large enough such that R_{pj}/n is less than the volume of the plasma occupied by the concentration wave entering the capillary bed, to obtain a good
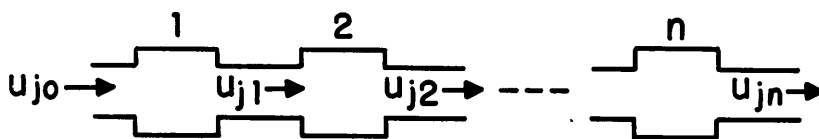

FIGURE 3

Diagram of n mixing chambers in series.

approximation to equations (1) and (2). This model has also been programmed for the IBM 704 [15] and has given reasonable results for the time course of concentration changes in the capillary plasma, extracellular space, and intracellular space. However, mixing in the circulation is slower than would be expected from experimental data on equilibration of dyes and I^{131}-labeled albumin after injection into the circulation [16], [17]. This is probably due both to the assumption of volume displacement flow and the use of only two organs with equal circulatory time lags. We would expect more rapid mixing in a many-organ model with a distribution of time lags. Although the required mixing in the circulation could be introduced arbitrarily by assuming a distribution of mixing chambers in the circulation, it would be more realistic and esthetically more satisfying to incorporate more of the known features of blood flow in the model of the circulation.

8. Discussion

The equations obtained from the model of drug distribution in a two-organ being are quite complex analytically. We would expect these difficulties to be multiplied manyfold in a model of a many-organ being which would be required if we wished to approximate the situation in a mammalian organism. Fortunately, the use of high-speed computers allows us to circumvent many of the analytical difficulties. Once we recognize this we can treat many biological problems in a more realistic fashion.

A projection of these concepts, which we believe will be of major importance for biological research, is the idea of experimentation with the computer. However, this is a useful concept only after fairly realistic models of a biological

system can be formulated. Once this stage has been reached we can consider running experiments on the model system with the computer. If this is done in conjunction with experiments on the real biological system one obtains a continuing feedback process between experiments on the model and on the real system which can lead to a great saving in time and experimental effort. Perhaps the most significant gain to be expected from such an approach is the clarification of basic concepts which must ensue since the setting up of the model system requires a rigorous formulation of our ideas about the basic mechanisms at work in the real system under study. Applying these ideas to a model of drug distribution, let us consider that we have a class of drugs whose biological effect is primarily due to a reaction with one component of the intracellular space. By a variation of parameters, the computer can then be used to study the effects of blood flow, permeability constants, and reaction rate constants on drug action. This would then provide criteria for picking or redesigning the drug for certain optimal effects. Similarly, experiments could be run to design optimal policies of drug administration.

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